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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

ART UNIT	PAPER NUMBER
1804	#15

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DATE MAILED: 07/21/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on April 17, 1997

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-40 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-40 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

★ U.S. GPO: 1996-404-496/40517

Claims 1, 9, 19, 29, and 40 have been amended by the response filed April 17, 1997. Regarding the amendment of claim 30 by the response by inserting --heterologous-- after "a" and before "gene" on line 3 of claim 30, the amendment is not entered because line 3 of claim 30 does not contain "a gene" as indicated in the response.

Claims 1-40 are pending.

The text of those sections of Title 35 U.S. Code not included in the action can be found in a prior Office action.

The amendment filed April 17, 1997 (Paper No. 14) is objected to under 35 U.S.C. 132 because it introduces **new matter** into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is the phrase "a heterologous gene essential for replication" as recited in claims 1, 19, 29, 30, and 40. The present application does not contain antecedent basis for the terminology nor does page 6, line 29 of the present application that is referred to in the present response contain nor define the terminology. Thus, this is **New Matter**.

Applicant is required to cancel the new matter in response to this Office action.

Claims 1-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject mater which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "a heterologous gene essential for replication of said vector" as recited in claim 1, line 3, for example, is not properly described in the application as filed because it is not apparent as to how said term is described in the disclosure of the application. While it is noted that applicants indicated that "support for the amendment can be found, *inter alia,* on page 6, line 29"; however, page 6 of the specification contains no disclosure of the phrase or of what to be considered as a heterologous gene essential for replication. The application only provides working examples demonstrating a construction of recombinant adenovirus vectors wherein a heterologous tissue-specific regulatory sequence operably linked to the E1A ORF and all of E1B genes is employed. Since the application does not provide any guidance to the artisan on how to employ a heterologous gene essential for replication of the claimed vector, said gene is under the control of a heterologous tissue-specific promoter, it is not apparent as to how the artisan can practice the claimed invention without undue experimentation.

Claims 9-18 are directed to a method of distributing a polynucleotide in a tissue *in vivo* using the claimed vectors. Claims 19-28, and 30-39 are directed to a cell containing the claimed vectors. The application on page 12 indicates that "the object of the distribution is to deliver the vector, gene product or the effects of the gene product (as by a bystander effect, for example) to substantially number of cells of the target tissue, so as to treat substantially the entire target tissue". Furthermore, the application on page 26 discloses that autologous cells transfected by the claimed vector are reinfused into the patient for generating a therapeutic effect. Thus, the claims

encompass gene-targeted therapy in any subject including a human and implanted cells containing the claimed vector for generating a therapeutic effect. Major considerations for any gene transfer or gene therapy protocol involve issues such as amount of DNA constructs to be administered, what amount is considered to be therapeutically effective for all of the claimed nucleic acid molecules, the route and time course of administration, the sites of administration, successful uptake of the claimed DNAs at the target site, expression of the DNAs at the target site in amounts of effecting the claimed methods (Crystal, Science, Vol. 270:404-409, 1995; Coghlan, New Scientists, Vol. 148:14-15, 1995). Gunzburg *et al.* (Molecular Medicine Today, pp. 410-417, 1995) state that "clearly, there are many problems to be overcome before gene therapy becomes a widely used treatment , and it will probably only ever complement rather than replace existing therapies" (p. 417). Gunzburg *et al.* also state that "the efficiency of gene delivery is perhaps the most limiting technical problem; this will require extensive modifications to existing vector systems or even the construction and development of new gene delivery systems (p. 416, column 2, last paragraph). Regarding the state of the art of gene therapy for human cancer, Mastrangelo *et al.* (Seminars in Oncology, Vol. 23, No. 1:4-21, 1996) states that "to date the major successes with gene therapy for cancer have been limited to *in vitro* systems where tumor cells with well defined genetic defects are easily targeted" (p. 13, column 2). Mastrangelo *et al.* further state that "Critical to the success of gene therapy is the efficient transfer (transfixing) of a functioning gene to the target cell" and that "this has prevented a major stumbling block, particularly for *in vivo* gene transfer" (p. 10, column 1). Regarding *ex*

vivo gene therapy, Mastrangelo *et al.* disclose that adoptive immunotherapy (e.g. infusion of cytotoxic cells such as genetically modified macrophage cells), which has been known to be effective *in vitro*, is not necessarily effective *in vivo* (pp. 18-19). Ledley (Human Gene Therapy 6:1129-1144, 1995) states that "every somatic target exhibits distinct properties, and the rate-limiting steps in gene delivery and expression may be expected to be different" and that "it is unlikely that any one method for gene transfer will prove to be effective in every organ" (p. 1139). Thus, without guidance from the specification the artisan would have been required practice undue experimentation to construct and use the claimed vectors.

In view of the lack of guidance regarding the administration parameters, lack of convincing data or working examples, breadth of the claims, state of the art and the unpredictability of the art, as set forth by the evidence presented above, undue experimentation would be required by one of ordinary skill to practice the invention as claimed.

The comments regarding the 112, first paragraph issues in the response of April 17, 1997 have been considered (pp. 2-13) but they are not persuasive for the reasons indicated in this Office Action.

In response to applicant's assertion that "it is not required to amend the disclosure to include the material incorporated by reference" (p. 3) and that "enablement in the present case does not depend upon the preparation of a specific plasmid, since the isolation and assaying of promoters with various kinds of coding sequences was routine in the art at the time the application was filed" (p.3), the comments are persuasive.

In response to applicant's assertion that "insufficient evidence has been offered to support the conclusion that the invention is sufficiently unpredictable that it is not enabled to any degrees" (p. 5), the comments persuasive regarding the original claims directed to vector constructs and methods of making the constructs.

In response to applicant's assertion that "no evidence or scientific reason has been presented that would support the position that it is not reasonably predictable that a promoter operably linked to such a coding sequence could not have been made or used without an undue burden of experimentation" (p. 6), and that the Dillon reference is not germane to the claimed invention (p. 7), and that "none of the claims is even related to levels of expression or gene therapy" (p. 7), the comments are not persuasive. While the specification is enabled for original claims directed to expression vectors and methods of making the vectors, the specification is not enabled for claims directed to cells containing the claimed vectors, and to methods for distributing a polynucleotide *in vivo,* since claims directed to cells and methods of use do encompass targeted gene therapy wherein a therapeutic response is generated in any subject, particularly given the reasons set forth in this Office action, and given the Dillon, Orkin and Motulsky, Pennisi, Crystal, Coghlan, Gunzburg *et al.*, Mastrangelo *et al.,* and the Ledley references indicating that targeted gene therapy remains unpredictable. Furthermore, since claims 1, 9, 19, 29, 30, and 40 have been amended to contain the phrase "a heterologous gene essential for replication", the specification does not enable any of the claimed inventions in view of the reasons set forth in this Office action.

In response to applicant's assertion that "there is no reason why an appropriate coding sequence in a virus could not be operably linked to such a heterologous transcriptional control sequence (p. 8), the comments are persuasive.

In response to applicant's assertion that since the Shingu *et al.* reference (Appendix) indicated the effectiveness of viral treatment employing bovine entreroviruses in prolonging the life span of mice bearing human carcinoma cells, the Pennisi reference is not relevant to the unpredictability of the claimed invention, the comments are not persuasive. It is not apparent as to how the data obtained the Shingu *et al.* reference can be correlated to the claimed invention since applicants have not provided evidence that the materials and method steps employed in the reference are identical to the claimed invention and methods disclosed in the application. Furthermore, the Shingu *et al.* disclose the use of natural bovine enterovirus on rabbits with experimentally induced adult T cell leukaemia which is materially different than the claimed vectors. The Pennisi reference and other references cited in the previous and in this Office action do indicate that the use of recombinant vectors as carriers for a therapeutic gene in treating cancer in all animals including humans requires undue experimentation to achieve a therapeutic effect, particularly given the passages of the references cited in this Office action, and given the Crystal reference disclosing that "Humans are not simply large mice" (p. 409). Furthermore, since the pending claims read on the use of any viral construct to "distribute a DNA sequence" *in vivo* to generate a therapeutic effect, and since the preferred viral construct is an adenoviral construct according to the application (p. 29), the Pennisi reference is cited to indicate that the use of

adenoviral constructs to generate a therapeutic effect in a subject including a human remains unpredictable.

In response to applicant's assertion that "evidence submitted by the Examiner does not establish a *prima facie* case of nonenablement based on the rationale that the immune system would neutralize virus before it reached the target", the comments are not persuasive. Not only the passages cited from the references, as disclosed in the previous Office action, do support that anti-viral immune responses to adenoviral constructs is one of many obstacles for effecting a therapeutic response *in vivo*, the passages also indicate that level of genes expression and administration parameters using any viral vector for gene therapy remain unpredictable.

In response to applicant's assertion that "50% of the population could be treated even if neutralization were a problem" to the use of adenoviral constructs in a human patient" (p. 11), the comments are not persuasive. Applicant has not provided factual data demonstrating that the use of any of the claimed vectors are effective in effecting a therapeutic response in any subject including a human, particularly in view of the reasons set forth in the previous and in this Office action.

In response to applicant's assertion regarding a clinical trial involving replication competent adenovirus in head and neck cancer patients discussed recently at the Biological Society meeting held in Washington, DC and other clinical trials indicating that "the effect of neutralizing antibodies can be countered by sufficiently routine increase in viral load, *i.e.*, by out-titering any potentially problematic neutralizing antibodies" (p. 11 bridging p. 12), the comments

are not persuasive. It is not apparent as to how the data obtained the clinical studies can be correlated to the claimed invention since applicants have not provided evidence that the materials and method steps employed in the reference are identical to the claimed invention and methods disclosed in the application. Applicant has not provided any factual data indicating that it would not require undue experimentation for one skilled in the art to arrive at the use of any of the claimed constructs to effect a therapeutic response *in vivo,* as indicated above. In response to applicant's assertion that "replication can occur in humans to a significant extent even in the presence of prior antibodies against adenovirus" (p. 12, the comments are noted. However, applicant has not provided what is considered a significant level of replication that effect a therapeutic response *in vivo,* particularly since applicant also indicates that "patients having prior exposure to adenovirus can die of adenoviral infection" (p. 12), and since the art of record expresses doubt regarding the state of the art of targeted gene therapy, as indicated above.

In response to applicant's assertion that "intraperitoneal, intravenous, intratumoral, and hepatic artery injections of adenoviral vectors would be reasonably expected to provide efficient transduction of tumor cells", and that "a tumor specific replication competent adenovirus would be expected to be even more effective because the bovine enterovirus is not even-tumor-specific", and that "applicants have shown sufficient evidence to overcome the *prima facie* case and show why an undue burden of experimentation would not have been required to practice the claimed invention (p. 12 bridging p. 13), the comments are not persuasive. Applicant has not provided any factual data indicating that a level of transduction at any target cell *in vivo* using the claimed

vectors is s sufficient to generate a therapeutic response *in vivo* in any subject including a human, particularly in view of the doubts expressed by the art of record, and in view of the reasons set forth in this Office action.

Claims 1-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8, and 19-40 are indefinite in the recitation of the term "capable of" since it not clear as to what exactly encompassed by the term, and since "capable" is only "capacity" and does not indicate per se that tissue-specific replication occurred.

Claims 1-8, and 19-29, and 40 are indefinite in the recitation of "a heterologous gene essential for replication" since it is not apparent whether the gene is heterologous to the tissue-specific transcriptional regulatory sequence or to the vector itself.

Claim 5 is vague and indefinite since the claim refers to the method of claim 4; however claim 4 is not directed to a method claim. For the purpose of compact prosecution, it is assumed that claim 5 refers to the vector of claim 4.

Claims 10 and 11 are vague and indefinite since the claims refer to the vector of claim 9; however, claim 9 is directed to a method claim. For the purpose of compact prosecution, it is assumed that claims 9 and 10 refer to the method of claim 9.

Claims 19-28, and 30-39 are indefinite in the recitation of "a cell" since it is not apparent whether the cell is directed to an isolated cell or whether the cell is an implanted cell *in vivo*.

Claims 9-11-12, 17, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Huber *et al.* (EP 415,731A3).

Huber *et al.* disclose a method for distributing a thymidine kinase gene in a specific tissue, *e.g.*, cancerous tissue, comprising the use of a retroviral vector, wherein said vector comprise a 5' and 3' viral LTR sequence operably linked to a heterologous tissue specific regulatory sequence (p. 3 and 6). More specifically, the disclosed regulatory sequences of Huber *et al.* is alpha-fetoprotein, CEA, HER-2/neu, and tyrosine hydroxylase transcriptional regulatory sequence (p. 4).

Absent evidence to the contrary, the method of Huber *et al.* has all the properties cited in the claims.

Claims 1, 2, 4, 5, 8, 9, 10, 12-14, 17, 18, 19, 20, 22-24, 27-31, 33-35, and 38-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Scott *et al.* (WO 93/09239).

Scott *et al.* disclose hybrid parvovirus vectors, methods of producing and using said vectors (entire document). The hybrid parvovirus vectors which comprise a pair of AAV inverted terminal repeats (ITRs) which flank at least one cassette containing the p6 promoter of B19 parvovirus which directs cell-specific expression operably linked to a heterologous gene, *e.g.*, MDR gene or TNF gene (p. 9 bridginng p. 10, pp. 13 and 14). More specifically, Scott *et al.*

disclose the use of a transcriptional promoter of B19 to effect tissue-specific expression of heterologous sequences (p. 11). Methods of constructing and producing vectors and virions are disclosed in Examples 1-5. Absent evident to the contrary, the Scott *et al.* has all the properties cited in the claims.

Claims 1, 2, 4-10, 13-20, 22-27, 29-31, and 33-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Stratford-Perricaudet *et al.* (Human Gene Transfer, vol. 219:51-61, 1991).

Stratford-Perricaudet *et al.* disclose a method of producing adenoviral vectors for targeted gene therapy, *e.g.* targeting neurons *in vivo,* (entire document). Said vector comprises the ITR sequences, and packaging sequences from the AD5 genome (essential for replication) operably linked to the MLP/TPL from the AD2 genome (*e.g.,* which is essential for the transcription for late viral transcripts) followed by a heterologous gene and the E4 gene region which encodes a number of proteins that are involved in the regulation of late gene expression and in the shutoff of host protein synthesis (Fig. 2). Thus, the vectors of Stratford-Perricaudet *et al.* comprise the ITR and packaging sequences heterologous to the MLP/TPL regulatory sequence which also is essential for replication of the vectors, and absent evident to the contrary the vectors have all the propertices cited in the claims.

Claims 3, 11, 12, 21, 28, and 32 are rejected under 35 U.S.C. 103 as being unpatentable over Stratford-Perricaudet *et al.* and Huber *et al.*

Stratford-Perricaudet *et al.* is applied here as indicated above. Furthermore, Stratford-Perricuadet *et al.* disclose that "because adenovirus is capable of infecting a wide variety of cell types in culture, it may prove realistic to use such a vector to target any organ *in vivo* (p. 58), and that "the potential of this virus to accommodate a large piece of DNA and to express a gene in the absence of both viral and cellular replication make this virus an attractive gene transfer system" (p. 51, abstract).

Huber *et al.* teach the use of tissue-specific promoters for targeting toxic genes to cancerous cells. The disclosed regulatory sequences of Huber *et al.* is alpha-fetoprotein, CEA, HER-2/neu, and tyrosine hydroxylase transcriptional regulatory sequences (p. 4).

It would have been obvious for one of ordinary skill in the art at the time the invention was made to have modified the adenoviral vectors of Stratford-Perricaudet *et al.* by employing any of the tissue-specific promoters disclosed in Huber *et al.* to specifically target therapeutic gene to a tumor site, given the teaching of Stratford-Perricaudet *et al.* indicating the advantage of using adenoviral vectors as an expression vector for gene transfer protocols, and given the teaching of Huber *et al.* disclosing that by using expression vectors comprising a tissue specific promoter operably linked to a toxic gene *in vivo*, the vectors are effective for delivering the toxic gene to a target tissue for expression.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

The rejections under 35 U.S.C. 102(b) of claims 1, 2, 10, 19, 20, 22, 29-31, 33, and 40 as being anticipated by Ringold, of claims 8, 27, and 38 as being anticipated by Gunzburg *et al.*, and of claims 4-7, 23-26, and 34-37 as being anticipated by McCormick have been withdrawn in view of applicant's response and amendment.

The rejection of claim 28 under 35 U.S.C. 103(a) as being unpatentable over Gunzburg in view of Culver has been withdrawn in view of applicant's response and amendment.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Jacqueline Stone*, may be reached at **(703) 305-3153**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 304-0196**.

Christopher S. F. Low

CHRISTOPHER S. F. LOW
PRIMARY EXAMINER
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Dave Nguyen

July 22, 1997